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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/799,345	03/12/2004	Christopher T. Ritchlin	21108.0031U2	6683

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EXAMINER	
GABEL, GAILENE	

ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/799,345	RITCHLIN ET AL.	
	Examiner	Art Unit	
	GAILENE R. GABEL	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2009 and 29 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-21,23,24,26-28,30-33,35,37,40-44 and 46-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 12-16, 21, 23, 24, 26-28, 30, 31, 33, 35, 37, and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment and response filed February 20, 2009 and October 29, 2008 are acknowledged and have been entered. Claims 1, 2, 15, 26, 31, 33, 35, and 40 have been amended. Claim 22, 25, 29, 34, 36, 38, 39, and 45 have been cancelled. Claims 7-11, 17-20, 32, 41-44, and 46-93 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being claims drawn to a non-elected invention. Withdrawn claims 41-44 have also been amended. Accordingly, claims 1-21, 23, 24, 26-28, 30-33, 35, 37, 40-44, and 46-93 are pending. Claims 1-6, 12-16, 21, 23, 24, 26-28, 30, 31, 33, 35, 37, and 40 are under examination.

Withdrawn Objections / Rejections

2. All rejections or objections not reiterated herein, have been withdrawn.

3. The rejections of claims 22, 25, 29, 34, 36, 38, 39, and 45 are now moot in light of Applicant's cancellation of the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-6, 12-16, 21, 23, 24, 26-28, 30, 31, and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, as amended, is vague and indefinite in reciting, “relative to a control subject” because it fails to clearly define what is encompassed in the term “control subject” especially relative to an individual being diagnosed for erosive arthritis. Herein, the recitation of “control subject” appears to encompass normal and abnormal control subjects.

Claim 15 is ambiguous in reciting, “more” because "more" is a relative term which lacks a comparative basis for defining its metes and bounds. The term "more" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 33 is indefinite in reciting, “more” because "more" is a relative term which lacks a comparative basis for defining its metes and bounds, albeit recited to be comparative to a control subject. Specifically, claim 33 fails to specifically define what threshold levels of OCP, i.e. how much more, are required to be measured in order to determine the presence of IJD. Additionally, claim 33 fails to make clear as to whether the control should be a normal (healthy) control of an abnormal control. Lastly, the recitation of “[presence of] disease” lacks clear antecedent basis.

Double Patenting

5. Claims 1-3, 12-16, 21-26, and 33-36 of this application conflict with claims 1-3, 11-13, 15, 16, 21-26, 33-36 of Application No. 10/548,389. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822. Applicant acknowledges the rejection. For reasons of record, this rejection under 37 CFR 1.78(b) is, hereby, maintained.

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

6. Claims 1-3, 12-16, 21-26, and 33-36 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-3, 11-13, 15, 16, 21-26, 33-36 of copending Application No. 10/548,839. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented. Applicant

acknowledges the rejection. For reasons of record, this statutory double patenting rejection is, hereby, maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

7. Claims 1-6, 12, 14, 21, 23, 24, 28, 30, 35, 40, and 49 are rejected under 35 U.S.C. 102(a) as being anticipated by Hirayama et al. (Osteoclast formation and activity in the pathogenesis of osteoporosis in Rheumatoid Arthritis, Rheumatology 41: 1232-1239 (2002)).

Hirayama et al. provide that Rheumatoid Arthritis (RA) is manifested as increased bone resorption by osteoclasts; hence, analyzed osteoclast formation from circulating precursors in RA patients (see Abstract). According to Hirayama et al., RA patients show bone erosion (erosive arthritis) on radiograph which is manifested as lower bone mineral density (p. 1232, col. 1). In practice, Hirayama et al. teach collecting blood sample from patients and normal subjects into heparinized tubes. Thereafter, peripheral blood mononuclear cells (PBMC) are collected and isolated by allowing them to settle in Ficoll-Hypaque gradient centrifugation. The PBMC cell preparations were fixed and stained histochemcally for tartrate resistant acid

phosphatase (TRAP) and immunohistochemically with monoclonal antibody against CD14. The number of stained multinucleated TRAP positive cells were counted and compared to normal control samples, so as to provide indication of osteoclast formation in RA patients. Hirayama et al. teach culturing the PBMCs with or without exogenous addition of M-CSF and RANKL (p. 1233, cols. 1 -2). According to Hirayama et al. osteoclasts are specialized multinucleated cells which carry out bone resorption; they are formed from mononuclear precursors that circulate in the monocyte fraction of peripheral blood. These mononuclear precursors express the monocyte/macrophage antigens CD11b and CD14, and are entirely negative for phenotypic markers for osteoclasts including TRAP and entirely lack the ability to carry out bone resorption. It has been shown, however, that CD14 positive cells in the monocyte fraction which express the receptor activator nuclear factor kB (RANK), can differentiate into functional osteoclasts in the presence of cells that express macrophage colony-stimulating factor (M-CSF) and RANK ligand including osteoblasts (p. 1232, col. 2 – p. 1233, col.1).

8. Claims 1-5, 12, 14, 21, 23, 24, 26-28, and 35 are rejected under 35 U.S.C. 102(a) as being anticipated by Jevon et al. (Osteoclast formation from circulating precursors in Osteoporosis, Scand J Rheumatol 32: 95-100 (January 1, 2003)).

Jevon et al. provide that there is imbalance between bone formation and bone resorption that underlie the pathogenesis of reduced bone mass (erosive arthritis) in osteoporosis; hence aim to determine the role of osteoclast formation using patients having bone and joint disorders. According to Jevon et a., bone resorption is carried out by osteoclasts which are formed from marrow-derived cells that circulate in the

monocyte fraction. In practice, Jevon et al. teach collecting blood sample from patient and normal subjects and isolating peripheral blood mononuclear cells (PBMC) by allowing them to settle in gradient centrifugation (Abstract and p. 95, col. 2 - p. 96, col. 1). The cell preparations were fixed and stained histochemcally for tartrate resistant acid phosphatase (TRAP) and immunohistochemically with monoclonal antibody against CD14 and CD51. The number of stained multinucleated TRAP positive cells (TRAP activity) containing three or more nuclei were counted and compared to normal control samples so as to provide indication of osteoclast formation. Jevon et al. teach culturing the PBMCs with or without exogenous addition of M-CSF (p.96, col. 2).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 13, 15, 16, 31, 33, 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hirayama et al. (Osteoclast formation and activity in the pathogenesis of osteoporosis in Rheumatoid Arthritis, Rheumatology 41: 1232-1239 (2002)) in view of Li et al. (Systemic TNFa Promotes Erosive Bone Resorption by Increasing the Number of CD11b+ Osteoclast Progenitors in the Periphery which are Dependent on RANK Signaling of Osteoclastogenesis, Journal of Bone and Mineral Research: JBMR Program and Abstracts (2002)).

Hirayama et al. differ from the claimed invention in failing to teach detecting and analyzing CD11b by fluorescence activated cell sorting (FACS).

Li et al. teach that TNFa is a potent osteoclastogenic factor shown to act directly on cells in osteoclast lineage, or indirectly by affecting the production of the essential osteoclast differentiation factor RANKL by osteoblasts. Li et al. studied the effect of chronic TNFa exposure to osteoclast precursor (OCP) differentiation and the requirement of RANK/RANKL in the process and found that the number and frequency of OCP expressing CD11b is increased. OCP cells expressing CD11b are detected and sorted using FACS. Li et al. suggested that CD11b may be used as marker of osteoclast progenitors.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Li into the method of Hirayama and detect CD11b cells using FACS to analyze CD11b expression in the OCPs because

FACS is well-known in the art for its multiparametric detection capability and conventionally used for its accuracy in specifically identifying and separating cells based on cell surface antigen expression. One of ordinary skill in the art at the time of the instant invention would have been motivated to incorporate the teaching of Li in increased expression of CD11b in OCP found in inflamed arthritic joints so as to be used as specific marker for OCP progenitors in IJD such as RA in the method of Hirayama because Hirayama found that OCPs correlate directly to increased osteoclast functional activity in RA whereupon inflamed arthritic joints manifest bone erosion surfaces; hence, providing fast accurate procedure in detecting OCPs in PBMCs of RA patients.

Response to Arguments

10. Applicant's arguments filed February 20, 2009 have been fully considered but they are not persuasive.

A) Applicant argues that the term “more" in claims 15 and 33 are definite because it is within to simply count the number of cells in both the subject and the control sample.

Applicant’s argument is not persuasive because the issue is not as to whether one skilled in the art can count more or less of the cells in the subject and the control sample but rather; what is lacking is the basis of how much more in number of multinucleated cells should be found in the subject in comparison to the [normal] control so as to provide indication of erosive arthritis in this method of diagnosing a subject with

erosive arthritis. Does Applicant intend that a single more multinucleated cell in the subject provides positive indication of erosive arthritis? In addition, it is also noted that claim 1 has also failed to clearly define what is encompassed in the "control subject" in this method of diagnosing erosive arthritis using the number of counted multinucleated cells.

B) Applicant argues that claims 1 and 26 have been amended to recite correlating the number of OCP in the subject with the presence of erosive arthritis; hence, Hirayama does not anticipate the claimed invention in failing to teach correlating OCP to erosive arthritis.

Contrary to Applicant's argument, Hirayama teaches the correlation between OCP and erosive arthritis manifested as bone erosion in page 1232, column 1; therefore, Hirayama is deemed to anticipate the claimed invention.

Regarding the interpretive "wherein" clause recited in claims 1 and 26 ("wherein an increase in the number of OCP in the subject relative to a control subject indicates the presence of erosive arthritis"), the clause does not recite any additional active method steps, but simply states a characterization or conclusion of the results of those steps. Therefore, the "wherein" clause is not considered to further limit the method defined by the claim and has not been given weight in construing the claims. See Texas Instruments, Inc. v. International Trade Comm., 988 F.2d 1165, 1171, 26 USPQ2d 1018, 1023 (Fed Cir. 1993) ("A 'whereby' clause that merely states the result of the limitations in the claim adds nothing to the patentability or substance of the claim."). See

also Minton v. National Assoc. of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003) ("A whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.").

C) Applicant argues that claims 1 and 26 have been amended to recite correlating the number of OCP in the subject with the presence of erosive arthritis; hence, Jevon et al. does not anticipate the claimed invention in failing to teach correlating OCP to erosive arthritis.

Contrary to Applicant's argument, Jevon teaches the correlation between OCP and erosive arthritis manifested as reduced bone mass in Abstract and p. 95, col. 2 - p. 96, col. 1; therefore, Jevon is deemed to anticipate the claimed invention.

Regarding the interpretive "wherein" clause recited in claims 1 and 26 ("wherein an increase in the number of OCP in the subject relative to a control subject indicates the presence of erosive arthritis"), the clause does not recite any additional active method steps, but simply states a characterization or conclusion of the results of those steps. Therefore, the "wherein" clause is not considered to further limit the method defined by the claim and has not been given weight in construing the claims. See Texas Instruments, Inc. v. International Trade Comm., 988 F.2d 1165, 1171, 26 USPQ2d 1018, 1023 (Fed Cir. 1993) ("A 'whereby' clause that merely states the result of the limitations in the claim adds nothing to the patentability or substance of the claim."). See also Minton v. National Assoc. of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67

USPQ2d 1614, 1620 (Fed. Cir. 2003) ("A whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.").

11. No claims are allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to GAILENE R. GABEL whose telephone number is

(571)272-0820. The examiner can normally be reached on Monday, Tuesday, Thursday, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark L. Shibuya can be reached on (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/GAILENE R. GABEL/
Primary Examiner, Art Unit 1641

May 20, 2009